

Public Statement, Food And Drug Advisory Committee Meeting on the approval of Xyrem
(gamma hydroxybutyrate)

My name is Dr. Deborah Zvosec. My research is in the area of gamma hydroxybutyrate (GHB) abuse, toxicity, addiction and withdrawal. Dr. Stephen Smith and I, with others, published a case series in Morbidity and Mortality Weekly Report in February 1999, describing adverse events due to ingestion of "dietary supplements" containing gamma butyrolactone (GBL). I was the lead author of a case series of 1,4 butanediol toxicity that was published in The New England Journal of Medicine in January 2001; toxicity episodes included 2 deaths that occurred with no co-intoxicants and no evidence of aspiration or asphyxiation or adulterants. Among the many health risks of GHB that I could describe to you today, I will focus on GHB addiction. In the course of our work, my name and Dr. Smith's name were listed on the Project GHB help site. We have received calls from over 40 addicted patients from 25 states and have treated an additional 5 cases of inpatient withdrawal at Hennepin County Medical Center in Minneapolis.

The majority of these addicted individuals began using GHB to treat insomnia, anxiety, depression, chemical dependence, or for bodybuilding purposes, as recommended by product marketers, web sites, and fringe pro-GHB physicians such as Dr. Ward Dean, author of "GHB, The Natural Mood Enhancer." Our patients began with small doses, often only at night, and discovered that it made them feel very good. They increased dosing frequency and, as tolerance developed, they needed more GHB in order to feel good; within months, they were taking GHB every 1-3 hours around the clock to avoid withdrawal symptoms. By the time they realized that they might be physically dependent, attempts to abstain resulted in severe anxiety, insomnia, panic attacks, and hallucinations. Their addiction destroyed their lives: they lost their spouses; they lost access to their children; they lost their jobs; they acquired tremendous debt to support their habit; and they became comatose while driving and crashed their cars, frequently on multiple occasions, and often causing injury and sometimes death. They called us in absolute desperation. We helped with locating and consulting with a physician on their inpatient detoxification. Detoxification was frequently similar to the worst cases of delirium tremens, requiring large, and often massive, doses of sedatives, often with intubation.

Almost all patients suffered weeks or months of profound depression and anxiety after detoxification and some also experienced muscle twitching and tremors. Of the over 40 patients we have worked with, only a handful have remained GHB-free, frequently despite chemical dependency treatment. Many have detoxified numerous times but continue to relapse, sometimes within hours of release from treatment. Unfortunately, many never lost faith in GHB and continued to be convinced that they could get back on G and use this wonder drug responsibly. They continue to argue its health benefits.

One of our patients was a 50-year-old businessman who used GHB for 5 years, initiating use to enhance bodybuilding and increasing to around the clock dosing within 2-3 months. His life was entirely controlled by the need to have GHB with him at all times. He had tried numerous times to quit. His wife was unaware of his addiction. She described witnessing frequent, frightening hypnotic states punctuated with clonic movements. She believed that his frequent states of apparent somnambulism were due to a sleep disorder, but despaired when a sleep specialist could not cure him. This woman is a very bright professional who was totally unaware of GHB, as is the case with many family members of GHB users. It was only on the morning of his admission for withdrawal that she learned the truth. After 6 days of detoxification with diazepam, he was through the worst of the hallucinations and appeared to be on the road to recovery. A psychiatrist treated him with sleeping medications and antidepressants, but within 3 days, he began using GHB again to control profound anxiety attacks and depression.

It has been the same story over and over. Few who have ventured deep enough into GHB have been able to emerge again, and when they do, neither they nor their families emerge unscathed.

GHB is perhaps the most addictive drug ever abused. Experienced drug users describe a euphoria that surpasses that of any other drug. Availability by off-label prescription presents profound personal and public health risks. The fringe physicians who now promote GHB will be joined by thousands of mainstream physicians, with the approval of the FDA. The majority of physicians are ignorant of the diverse health risks of GHB, as are toxicologists and law enforcement officials. Users will seek Xyrem from physicians who don't recognize "sodium oxybate" as GHB and are unfamiliar with the health risks. Patients will obtain Xyrem prescriptions for fake sleep disorders, and for insomnia, fibromyalgia, depression, anxiety, and other conditions for which it has been touted.

We know that addicts often use GHB and its analogs interchangeably; their compound of choice is dependent on access, which is determined by cost, perceived quality, ease of procurement, and legal status.

Clinical literature reports an addicted user who spent up to \$200 per day for GHB (over \$70,000 per year). Our patients have reported ingestion of up to a bottle of supplement/solvent product every 1-2 days, at \$60-100 per bottle (\$11,000-\$36,000 per year). A Xyrem prescription will be a bargain for such users, who will then avoid the high prices, erratic availability, and risks of supplement and solvent purchase. We know that many people are afraid to buy or make their own cheap GHB, due to risks of contamination or errors of production. Xyrem, a pharmaceutical product of controlled quality, available by legal prescription, and with very little risk if found in their possession, will be very attractive to such users. We know that users are watching for the release of Xyrem. Recreational drug sites post links to narcolepsy sites and publications about Xyrem; hotyellow98.com, for example, instructed "click here to find out when GHB will be released under the trade name of Xyrem."

There is no systematic federal, state, or local data on the demographics, epidemiology, use patterns, or costs of GHB abuse or addiction. Adverse events are vastly underreported because: 1) we have no field test to detect GHB; 2) we have no routine hospital toxicology screening test for GHB; 3) most clinicians and toxicologists do not know to look for GHB and it is easily masked by or confused with other intoxications; and 4) we have no systematic reporting mechanism accessible to all practitioners. Furthermore, we have no data on chronic or long-term effects of frequent use and addiction. No federal or state funds have been spent on research, education, or prevention of GHB-related health risks in the general public. There are no treatment protocols that have been scientifically validated for either acute GHB toxicity or severe withdrawal, both of which are highly variable and extremely unpredictable.

The nature and course of the Xyrem approval process troubles me deeply. In contradiction to past procedures, the determination of Schedule III status for medically-used GHB occurred prior to discussion of scientific proof of safety and efficacy. Release of Xyrem for off-label prescription, at this time, to a distribution system that uses voluntary self-monitoring with no mandatory governmental oversight or regulation is madness. I urge you to maintain Xyrem/GHB under research status so that narcolepsy patients may receive their medications until an externally monitored and regulated prescription and distribution system may be established. Potential repercussions of ill-advised or premature action are profound. Precedent has already been broken with this split scheduling. It must be broken again if we hope to avoid learning from more tragic mistakes.

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